Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF Moriarty, R.M.; Penmasta, R.; Guo, L.; Rao, M.S.; and Mehta, R.G.	)	Docket No. SYN1
SERIAL NO.: 09/008,957	)	Group No. 1616
FILED: Jan. 20, 1998	)	Examiner: Badio
TITLE: 1α-HYDROXYVITAMIN D_5, ITS SYNTHESIS AND USE IN CANCER PREVENTION AND THERAPY	)	Date: August 8, 2001

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

APPELLANTS' REPLY BRIEF

I. STATUS OF THE APPEAL

This is an appeal from the decision of the Primary Examiner dated November 30, 2000, as supplemented by an Advisory Action dated February 9, 2001. A Notice of Appeal accompanied by the required fee was timely filed on February 22, 2001. Appellants' Brief on Appeal was filed April 23, 2001. The Examiner's Answer, mailed June 8, 2001, maintained the rejection of claim 1 under 35 U.S.C. § 103. Appellants respectfully traverse this rejection.

II. STATUS OF CLAIMS

Claims 1-19 are pending in the case. Claims 7-9 have been withdrawn from consideration as directed to a separate invention. Claims 1-6 and 10-19 stand rejected under 35 U.S.C. § 103.

Appellants appeal the rejection of Claim 1 only. A copy of claim 1 is attached to Appellants' Brief submitted April 23, 2001.

III. ARGUMENT

Claim 1 is directed to the novel vitamin D compound $1\alpha(OH)D_5$. In her Answer the Examiner maintains her rejection of claim 1 as being unpatentable over Holick et al. '643 and '538, Bishop et al. '429 and Gulbrandsen et al. '790. The Examiner's argument can be summed up by quoting the following statement in her Answer:

> "In summary, (1) the compound is encompassed by the prior art genus; (2) the prior art makes obvious the lower calcemic property of the claimed compound; and (3) applicant's declarations do not show any unexpected result because the ordinary artisan would expect differences in the degree to which each compound encompassed by the prior art genus alters calcium metabolism."

There is no disagreement that Appellants' claimed compound (along with hundreds of other compounds) is encompassed by the genus disclosed in the prior art references. There is also no disagreement that Appellants' compound exhibits statistically significantly lower calcemic activity than its closest prior art compound, $1\alpha(OH)$ vitamin D4, as evidenced in Appellants' declarations by Moriarty and Hedayat. However, Appellants strongly disagree that the prior art makes obvious the lower calcemic activity of $1\alpha(OH)D_5$ and that Appellants' declarations do not show any unexpected result.

The crux of the disagreement between the parties lies in

whether, in view of the entire body of prior art, a person of ordinary skill in the art at the time of the invention would have expected 1α(OH)D_5 to have such low calcemic activity as Appellants have shown it to have[1]. The Examiner continues to assert that 1α(OH)D_5's low level of calcemic activity was not unexpected in view of Bishop et al. U.S. Patent 5,763,429 at col. 5, line 60 to col. 6, line 14. There Bishop states that "[t]he 1α-hydroxyvitamin D compounds of formula I of the present invention are those that ... have a lower tendency or inability to cause hypercalcemia and/or hypercalcuria [than the vitamin D3 compounds]."

Appellants assert that Bishop's statement is mere speculation unsupported by any data, that it is in fact incorrect, that there exist 1α-hydroxyvitamin D compounds of Bishop formula I that exhibit the same or higher calcemic activity than vitamin D3, and that, most importantly, in view of the entire body of prior art available at the time of Appellants' invention, including, especially, Knutson U.S. Patent No. 5,488,120, a person of ordinary skill in the art would not have expected 1α(OH)D_5 to have such a low level of calcemic activity as Appellants found it to have.

Bishop's Statement Would Not Have Been Accepted At Face Value By A Skilled Artisan, As The Examiner Has Assumed

In the case of a prior art reference disclosing a genus, the

[1] As discussed infra, this lower calcemic activity, coupled with its anti-carcinogenic properties, makes 1α(OH)D_5 markedly superior to other vitamin D

predictability of the art and the number of species encompassed by the genus are two of the factors that should be taken into account in making a determination of obviousness. MPEP § 2144.08 II(A)(1). Given the large size of the genus disclosed by the prior art and the unpredictability of the art, the skilled artisan would not have taken Bishop's statement at face value, as the Examiner has done throughout this prosecution. Rather, the skilled artisan would have weighed Bishop's statement against the entire body of information available, including the Knutson '120 patent. In doing so, the skilled artisan would have found that not all 1α-hydroxyvitamin D compounds of Bishop formula (I) have a lower tendency to cause calcemia than vitamin D3, as Bishop states, and certainly not as low as $1\alpha(OH)D_5$.

For evidence that Bishop's statement is wrong, or that, at the very least, the art is unpredictable, the skilled artisan would not have had to search any further than the '120 patent awarded to Dr. Joyce Knutson, one of the named inventors on the Bishop patent. The Knutson '120 patent at col. 6, lines 29-32 teaches that 1α(OH) vitamin D4 (another compound belonging to the genus disclosed in Bishop) is effective at <u>increasing</u> serum calcium in vitamin D deficient rats, which would appear to contradict Bishop's statement that all vitamin D compounds belonging to the genus disclosed in Bishop have a lower tendency to cause calcemia. Moreover, the publicly available file history

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analogues in the prevention and treatment of certain types of cancer.

of the '120 patent contains data showing that $1\alpha(OH)D_4$, rather than having lower calcemic activity than vitamin D3, actually has essentially the same effect on serum calcium as $1\alpha(OH)D_3$ and $1\alpha,25(OH)_2D_3$. This is a direct contradiction of the Bishop statement.

Bishop cites the Knutson '120 patent as teaching a means for synthesizing compounds of formula I (Bishop at col. 6, lines 41-45). This fact and the fact that Dr. Knutson is a named inventor on the Bishop patent would suggest that the authors of Bishop et al. should have known better than to make such a sweeping - and factually incorrect - statement. Regardless of why the statement was made, the point remains that a skilled artisan would not have taken such a broad statement at face value, but would have looked to other references before drawing a conclusion about the expected relative calcemic activity of $1\alpha(OH)D_5$. And when Bishop's statement is considered along with Knutson's own publicly available teachings, there is no clear expectation that $1\alpha(OH)D_5$ would have a lower tendency to cause calcemia than vitamin D3, much less to the extent discovered by Appellants.

$1\alpha(OH)D5$ Exhibits Unexpectedly Improved Properties Not Present In The Prior Art

The Examiner has made a prima facie case of obviousness by citing a reference that discloses a generic group of vitamin D derivatives that includes Appellants' claimed compound. However, a prima facie case of obviousness may be rebutted with evidence

that the claimed compound possesses unexpectedly improved properties or properties not present in the prior art. MPEP §2144.08 II(B), citing Dillon, 919 F.2d at 692-93, 16 USPQ2d at 1901.

In developing $1\alpha(OH)D_4$, Dr. Knutson and her colleagues were searching for a vitamin D compound of low toxicity that could be used as a therapeutic agent for treating disorders of calcium metabolism (col. 2, lines 9-11). In other words, they were searching for a compound that had essentially the same high calcium retaining ability as vitamin D3 but with lower toxicity.

During the prosecution of the vitamin D4 application, Dr. Knutson argued that $1\alpha(OH)D_4$ is "essentially equivalent to $1\alpha(OH)D_3$ and $1\alpha,25(OH)_2D_3$ in its ability to stimulate an increase in serum calcium." (Declaration Under 37 CFR 1.132 by Joyce Knutson dated August 4, 1994.) Unlike Bishop, who provides no data to support his statement at Bishop col. 5 to col. 6, Dr. Knutson presents a side-by-side comparison of vitamin D4 and vitamin D3 to support her statement of equivalency.

The Knutson patent and file wrapper teach that $1\alpha(OH)D_4$, $1\alpha(OH)D_3$ and $1\alpha,25(OH)_2D_3$ have essentially the same calcium activity. In view of this teaching, even when Bishop's statement is considered, a skilled artisan would more likely have expected that $1\alpha(OH)D5$ would have about the same calcemic activity as its closest vitamin D analogues. Surprisingly and unexpectedly, it does not.

Appellants Were The First To Synthesize 1α(OH)D5

In response to Appellants' assertion that there were no known methods for synthesizing $1\alpha(OH)D_5$ (and therefore the presumption of obvious is overcome), the Examiner argues that, since the prior art makes structurally similar compounds, the ordinary artisan would be able to make the claimed compound utilizing a process taught in the cited art. Appellants strongly disagree. As Appellants explained in their Brief on Appeal, it was not possible to make $1\alpha(OH)D_5$ as taught in the cited art precisely because the raw material to make it, systosterol, was not commercially available in pure form. It took Appellants' ingenuity to find a method for synthesizing $1\alpha(OH)D_5$ using an entirely new route.

Secondary Considerations Support a Finding of Patentability

Secondary considerations aid in determining under section 103 the state of the art at the time the invention was made. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 USPQ 543, 552 (Fed. Cir. 1985). For instance, the fact that experts at the time of the invention perceived it as an exceptional technological advance is good evidence of nonobviousness. Id. At 551-552.

Appellants have provided evidence that a number of highly respected experts, at the time the present invention was made, perceived it as an exceptional achievement. For instance, Appellants provided an Editorial by Drs. Moray J. Campbell and H.

Phillip Koeffler of the Division of Hematology/Oncology at Cedars-Sinai Medical Center/UCLA School of Medicine that appeared in the Journal of the National Cancer Institute, Vol. 89, No. 3 (Feb. 5, 1997) that stated in part: "A major focus of chemopreventive research in the field of vitamin D and cancer has been to synthesize analogues of $1\alpha,25(OH)_2D_3$ that have prominent antiproliferative effects against cancer cells without resulting in hypercalcemia when they are administered in vivo at pharmacologically active doses....The study by Mehta et al. reported in this issue of the Journal presents an entirely novel class of vitamin D compounds ($1\alpha(OH)D_5$)...[T]he therapeutic index .. for this compound is sufficiently high to warrant further investigations .. " (See Attachment C to Appellants' Submission After Final Office Action filed Dec. 13, 1999.) This editorial is strong evidence of the novelty, long felt need, and therapeutic promise of Appellants' claimed compound.

Appellants also submitted an article that appeared three years later in the Journal of the National Cancer Institute, Vol. 92, No. 22 (November 15, 2000), entitled "Prevention of N-Methyl-N-Nitrosourea-Induced Mammary Carcenogenesis in Rats by 1α-Hydroxyvitamin D_5", and authored by some of the inventors of the present invention, wherein the authors explain that the use of the active form of vitamin D, $1\alpha,25(OH)_2D_3$, in cancer prevention and treatment is limited because it induces excessive blood calcium levels (hypercalcemia), but that $1\alpha(OH)D_5$ appears to be a

"good candidate for further development." (See Jan. 30, 1999 Amendment After Final) This article is further evidence that Appellants' compound appears to be superior to $1\alpha,25(OH)_2D_3$ for cancer prevention and treatment.

The fact that Appellants' compound has been the subject of an editorial and two articles in the Journal of the National Cancer Institute (JNCI) is itself strong evidence that the compound is perceived by those skilled in the art as exceptional. The JNCI is the best-rated cancer journal in the world, with an impact ratio better than any journal reporting cancer research. Articles submitted for publication in the JNCI are subject to a rigorous scientific review before acceptance for publication.

Still more evidence of the exceptional nature of Appellants' compound was provided in the Declaration of Dr. John E. Nelson, M.D., Ph.D., a clinical pharmacologist, in which Dr. Nelson states "In my opinion Applicants' 1α-hydroxyvitamin D_5 compound exhibits surprising properties that would not have been expected at the time the compound was first synthesized by Applicants." (See attachment to Appellants' July 8, 1999 Amendment.)

Still further evidence that Appellants' compound is exceptional is shown by statements made by the United States Army Medical Research and Materiel Command (USAMRMC) in its December 8, 1998 "Peer Review Panel Report" (not part of the record in this case) written in response to a research grant request regarding $1\alpha(OH)D_5$. There, the USAMRMC stated that "the

preliminary results are highly promising" and that "[I]t seems likely that the distinguished investigators will produce informative results and possibly a new class of clinically valuable agents."

Appellants continue to invest considerable resources in the development of $1\alpha(OH)D_5$ for use in the prevention and treatment of cancer. The USAMRMC has provided significant funding for this continued work with $1\alpha(OH)D_5$. Appellants and the public should not be deprived of the fruits of their efforts and funding because of a single unsupported statement made in a single reference that runs contrary to other, better supported, teachings in the field.

SUMMARY OF APPELLANT'S ARGUMENT

While the fact that the claimed compound may be part of a larger genus raises a presumption of obviousness, that presumption has been more than adequately rebutted by evidence of the unexpectedly beneficial properties of $1\alpha(OH)D_5$ and by secondary considerations, such as experts' opinions as to the exceptional properties of $1\alpha(OH)D_5$ and its commercial promise. A decision reversing the Examiner's rejection of claim 1 is respectfully requested.

Respectfully submitted,

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